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# SOME RECENT CHEMICO-PHYSIOLOGICAL DISCOVERIES REGARDING THE CELL.[1]

BY R. H. CHITTENDEN.

In opening this discussion, or rather in making such remarks as seem appropriate in connection with the subject before us for consideration this morning, I am reminded that the chemistry and the chemical processes of the cell have received very little attention from the generality of biologists. This is perhaps natural, since the morphological side of biology has for many years presented a more attractive field for the majority of scientific workers, and the difficulties have not been so great as in the chemical and physiological problems awaiting solution.

Simplicity of structure, as embodied in the single cell of a unicellular organism, means to the physiologist increased complexity of function. In the higher organism with its many groups of cells, we can easily comprehend how one group may be characterized by one line of functional activity, while a neighboring group of cells in the form of another tissue or organ is endowed with functional activity of quite a different order. One group of cells is set apart for one line of duties, while another group has quite different functions; in other words, structural differentiation has begotten or accompanied chemical and functional differentiation. All this seems quite plausible, indeed, quite natural, but how shall we explain all the varied functions possessed by the unicellular organism unless we accept the idea of a possible chemical differentiation of the cell protoplasm inside the cell wall. Digestion, assimilation, excretion and reproduction are functions possessed alike by the unicellular organism and its higher neighbor the multicellular organism. In the latter, we recognize distinct groups of specially characterized cells for each phase and form of functional activity, each group as in a gland or tissue having a different chemical structure with its own peculiar line of chemical activity and its own particular katabolic products. In the unicellular organism, on the other hand, a differentiation of protoplasmic particles is the only plausible explanation of the diverse functions of the living cell.

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[1] The Introductory paper in a discussion of our present knowledge of the cell at the meeting of the American Society of Naturalists, New Haven, Dec. 28, 1893.

This being true we can no longer look on the cell as the ultimate unit of structure, certainly not from the chemical standpoint. The cell may be considered rather as a complex molecule, or series of molecules, built up of many morphological atoms or rather groups of atoms. Thus, the cytoplasm, for example, may be looked upon as a multitude or mass of living units of structure, as the plasomen of Wiesner. Call them what you will—plasomen, idiosomes, gemmules, plastidules, idioblasts or physiological units—these particles have the power of dividing, and, indeed, of growth and assimilation. Moreover, it is possible that this power of growth and reproduction may be independent, in part at least, of the cell nucleus and the constituent karyoplasm. Furthermore, the nucleus too may perhaps be considered as composed of auto-divisible organic individuals, these hypothetical particles, both of the cytoplasm and of the karyoplasm, being considered as the living atoms of the molecule, the last divisible living bodies of the cell.

For fifty years or more, the cell theory of structure and development as outlined by Schleiden and Schwann has been the nucleus for nearly all phases of biological work, and although our knowledge of the cell has advanced greatly in all directions during the last half-century, yet nearly all the problems of life are still viewed from the standpoint of the cell theory; morphological facts and physiological facts are all tested more or less by their relationship to cell structure and cell function. As Whitman[2] has aptly said "all the search-lights of the biological sciences have been turned upon the cell; it has been hunted up and down through every grade of organization; it has been searched inside and out, experimented upon, and studied in its manifold relations as a unit of form and function", and yet, if I understand the matter aright, many morphologists to-day are inclined to protest somewhat against "the complete ascendency of the cell as a unit of organization." We must not ignore the existence of the organic chemical compounds, with their peculiar molecular structure, which compose the cell protoplasm; the whole secret of organization, assimilation, growth, development, etc., may rest upon these ultimate elements of living matter. These may be the actual representatives of the physiological units of Herbert Spencer, or the plasomes of Wiesner; they may be the real units of all forms of living matter, the bearers of heredity and the true builders of the organism whether it be simple or complex. These protoplasmic particles are not necessarily limited in their action, or in the influence they exert, by cell walls or other boundaries.

The physiologist, however, like all other biologists, has been wont to look upon the cell as "the unit of the manifold variable forms of the organism" (Hammarsten), representing the seat of the many varied chemical processes characteristic of the individual tissues and organs. The cells naturally, through their variable activity, govern the range and intensity of the metabolic processes of the organism; but all this is simply a general expression of the idea that the chemical processes of the higher organism are localized in the cellular tissues of the body rather than in the adjacent fluids. It appears to me that we have every reason to believe in the existence of ultimate particles of living matter, both cytoplasm and karyoplasm, inside the cell, which are the real units of the organism. They may not be recognizable morphologically, but they exist nevertheless as individual links in that chain of molecules of which we believe living protoplasm to be composed. As Quincke[3] has recently said " bioiogical science must, well or ill, take into account the fact that the development of the cell and the life of organic nature depends on masses and layers which cannot be seen by the microscope alone." Hence, the chemistry of the cell offers an interesting field of work full of promise, although for the most part it has been studied mainly with a view to obtaining more light regarding the general metabolic processes of the higher organisms.

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[2] The inadequacy of the cell-theory of development. Journal of Morphology, Vol. 8, p. 639.

From a chemical standpoint, the living animal cell may be considered as a combination of varied chemical substances always in a state of unequilibrium, unstable in the highest degree, readily prone to break down by oxidation or cleavage into bodies of less complexity, each downward step in the process of disintegration, giving rise to the liberation of a certain amount of energy. These explosive, or it may be gradual, decompositions are going on continually as long as life endures, and chemical transformations and chemical decompositions are therefore an essential part of the life history of the cell, or of the organism of which it is an integral part. In them are hidden many of life's mysteries, and some of the most intricate as well as important phases of physiological phenomena are closely connected with these more or less obscure chemical transformations.

This constant liberation of energy, so characteristic of the living animal cell, coming as it does from the continued disintegration of the living substance of the organism creates a demand for fresh material to supply the place of that which has undergone this vital decay, otherwise the vital energies flag and the bodily structure withers away. The food material supplied to meet this demand, although it may be easily oxidizable or combustible cannot supply the needs of the organism without becoming vitalized. As dead, inert matter it is simply combustible; it can exhibit energy as heat only like other forms of organic matter, but its energy cannot be made available in the manner required by the living animal organism. It must first be fitted for assimilation through digestion or otherwise; after which, having passed into the circulating fluids, it finally reaches the cell under whose influence it undergoes a final change by which it is raised to a higher plane. That which was dead has become alive, a chemical transformation has occurred, the atoms in the molecule have been rearranged and we have to deal with living matter; a change accomplished through the anabolic power of the living cell, or better of the cell protoplasm. Anabolism and katabolism, construction and destruction, are thus going on continually in the living animal cell side by side as a necessary concomitant of life, but the processes are not everywhere of the same order. They are qualitatively and quantitatively unlike, especially the katabolic, the latter showing some peculiarities characteristic of almost every individual group of cells as comprised in individual organs or tissues. Each individual cell as a component of the many and varied tissues of the organism is to be compared to a well equipped chemical laboratory, the character and amount of the work produced being dependent in part upon the intrinsic qualities of the cell, *i. e.* of the cell protoplasm, and in part upon the nature of its surroundings or environment. While these statements apply more particularly to the animal cell, they are likewise true of the vegetable cell, the only difference being that in the latter we find a predominance of synthetical processes, a remarkable power of building up complex substances such as starch and proteid out of the simple food material obtained from the air and the soil, while the animal cell is especially characterized by the extent of its katabolic processes.

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[3] Nature. Vol. 49. p. 6.

It is thus very evident that while in the early stages of growth and development, all animal cells, for example, may show a striking similarity in composition, as soon as differentiation in form begins to manifest itself with an accompaniment of functional activity, chemical composition is gradually altered until at last each group of cells characteristic of the individual organs and tissues acquires a composition peculiar to itself. Obviously, however, the most striking differences are manifested in the character of the so-called secondary constituents of the cell protoplasm, *i. e.* the katabolic products of the cell's activity, such as the different enzymes or their antecedents, the albuminoids, pigments, fat, glycogen, etc., to which must be added the substratum of dead food material for the nutrition of the cell. From this very diversity in the character of the katabolic products of protoplasmic activity, we might easily argue corresponding differences in the character of the primary constituents of the cell protoplasm, which in turn would imply fundamental differences in the nature of the anabolic processes by which the cell protoplasm is formed.

It will be seen from what has just been said that it is not an easy matter to discriminate between the primary constituents of a cell and the so-called secondary constituents, or such as arise from the katabolic activity of the primary bodies. Furthermore, it is an extremely difficult matter to isolate from a given tissue or organ the active cells entering into its structure, or to collect together a sufficient number of unicellular organisms free from impurities or admixtures. When, however, this has been accomplished and we are ready to analyze the isolated cells, we are at once confronted with the limitations attending this kind of work, especially the fact that any ordinary method of separation or analysis, even the initiatory steps in the process, immediately transforms the living matter into dead matter, which transformation may be accompanied by cleavage or other chemical changes of more or less complexity; so that the bodies we identify as components of the cell protoplasm may be simply alteration products, or fragments of the larger and more complex molecules resident in the living matter.

From microscopical examination we have evidence that protoplasm is far from being homogeneous, that it is loaded with granules and pervaded by a mesh-work of irregular arrangement. These various forms of protoplasmic differentiation have, as you know, been variously named by different investigators, as the spongioplasm, paraplasm, hyaloplasm, etc., and we are led to infer marked differences in chemical composition from the behavior of the several parts of the cell toward the many pigments or dyes used in histological investigation. There can be no manner of doubt that the differences in color between the nucleus and the cytoplasm of the cell, for example, as brought out by the agency of various pigments is due to differences in chemical composition. Again, as you are well aware, Ehrlich has been able to discriminate between the different varieties of granules found in cell protoplasm by their behavior toward neutral, acid and alkaline aniline dyes. Thus, in the centresome we have a mass of differentiated cytoplasm, which as Watasé[4] has shown in the egg of Unio, may be made to stand out with great distinctness by means of acid-fuchsin, while the spindle fibres and the rays of the aster remain practically unstained, thus clearly pointing to differences in chemical composition which are well worthy of note. Again, there are still other granules frequently present in the cytoplasm of many cells, staining dark with osmic acid, which indicate still other differences in chemical composition. But our knowledge concerning the chemical nature of protoplasm is far too imperfect and scanty to admit of our drawing any other than the broadest generalizations from the affinity the protoplasm may show for various pigments.

Further, as you well know, the nuclear constituents have been divided by various investigators, as by Flemming, into several groups according to the action of different stains; thus, we have the chromatic substance or chromatin, which stains readily with the aniline dyes and which comprises especially the nuclear network, then achromatin, or that portion of the nucleus which does not stain readily, as the nuclear matrix and the nuclear membrane.

Such statements as these may be added to almost indefinitely, but for our purpose the above are amply sufficient to indicate the existence of marked chemical differences in the cell cytoplasm and karyoplasm. And, indeed, that is all they do indicate; they give us very little knowledge of the real nature of the substances which are the cause of these differences in reaction. We must have more definite chemical knowledge before we can hope to attain to a clearer understanding of the actual make up of cell protoplasm. Further, such knowledge is not to be obtained solely by micro-chemical study. The latter is surely important, but macroscopical methods must be relied upon mainly to furnish the desired information, and when we have full knowledge of the chemical nature of the substances present in the protoplasm, we may hope to find micro-chemical methods adapted to their accurate detection.

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[4] Homology of the Centresome. Journal of Morphology, Vol. 8, p. 433.

What now is the state of our knowledge regarding the primary constituents of cell protoplasm? Taking the results which have been elaborated by painstaking work during the last ten years, I think we are justified in asserting that the primary constituents of the cytoplasm are especially a peculiar group of proteid or albuminous bodies known as nucleo-albumins and characterized by containing phosphorus. These are by far the most numerous of the substances present in the cytoplasm. Next in importance are simple proteids belonging mainly to the group of globulins, a class of albuminous bodies insoluble in water but readily dissolved by 5–10 per cent. salt solution. Lecithin comes next, a complex phosphorized body having a constitution similar to that of a fat and yielding by decomposition higher fatty acids, glycero-phosphoric acid and cholin. This body is also insoluble in water and likewise in salt solution, but is readily dissolved by ether and somewhat by alcohol. Another substance almost invariably present in cytoplasm is cholesterin, a solid crystalline alcohol of somewhat uncertain constitution, insoluble in water and salt solution, but readily soluble in alcohol and ether. The remaining constituents of the cytoplasm are the inorganic elements calcium, magnesium, potassium and sodium united with chlorine and phosphoric acid to form chlorides and phosphates respectively. It may be somewhat questionable whether all of these latter salts are primary constituents of the cytoplasm, although it seems quite certain that potassium which is present in fairly large quantities in animal cells is a true primary constituent. Potassium phosphate is certainly of primary importance for the life and development of the animal cell, as no doubt also are the earthy phosphates, although we can hardly formulate how they exist in the cytoplasm unless it be in close union with the proteids or nucleo-albumins of the cell, for which we know they have a strong affinity. Again, it is to be remembered that the ash of all cells shows the presence of a certain amount of ferric oxide. This, however, does not come from ordinary iron salts present in the protoplasm, but the iron appears to exist in some peculiar organic combination, apparently united to carbon. It is especially to be noted as a component of so-called iron-containing nucleins, or nucleo-albumins.

It is thus seen that proteid matter in some one or more forms, mostly as nucleo-albumins, constitutes the great bulk of cytoplasm, and the typical anabolic product of the living cell is unquestionably represented by a molecule, or molecules, in which proteid matter occupies a prominent place. "But that the albumin molecule is alone the bearer of life and all the other constituents of the protoplasm its satellites we certainly cannot affirm." (Kossel)

Between the cytoplasm and the karyoplasm there is very little constant difference. The one typical constituent of the cell nucleus, however, is nuclein or one of the bodies of that group. It is important to note in this connection that such examinations as have been made show that the primary constituents of the cell may be located in the nucleus in great part, or they may be evenly distributed through both cytoplasm and karyoplasm, or indeed they may be almost wholly wanting in the nucleus, occurring only in the cytoplasm.[5] This latter condition offers a ready explanation of the well-known fact that cells rich in nuclei and consequently containing only a little cytoplasm, as the spermatozoa, are extremely poor in many of the primary bodies of ordinary cells. The one body, however, characteristic of the cell nucleus is nuclein.

Cholesterin and lecithin are certainly common to both cytoplasm and karyoplasm, being found abundantly in cells rich in nuclei as well as in cells poor in nuclear elements. We must reiterate, however, that the first place in importance among these so-called primary bodies is to be ascribed to the proteids in all living cells, for it seems more than probable that the nucleins and the lecithins found in cell protoplasm are constructed synthetically out of certain cleavage products of the proteids and phosphates. However this may be, the globulins, nucleo-albumins and nucleins are, so far as our present knowledge extends, the important constituents of cell protoplasm in all animal and vegetable cells. Of these three classes of bodies, the nucleins and the related nucleo-albumins are deserving of special notice.

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[5] Kossel. Verhandlungen d. physiol. Gesellschaft zu Berlin, Feb'y, 1890.

The substance originally known as nuclein and first identified by Hoppe-Seyler and Miescher as the main constituent of the nucleus of pus cells was prepared by a number of investigators from different kinds of material rich in nuclei, or nuclear substance. Thus, Miescher prepared it from the spermatozoa of different animals, Geoghegan from the brain, Hoppe-Seyler from yeast cells, Plósz from the liver and von Jaksch from the human brain. The products obtained, however, while showing certain points in common, were unlike each other in many respects. Thus, they were all alike in containing a noticeable amount of phosphorus, but the percentage of phosphorus was found on analysis to vary from 1.8 per cent. up to 9.5 per cent. Again, the several products differed in their degree of solubility in alkalies, some being very soluble and others only slightly so. These marked discrepancies were naturally considered as implying that the so-called nuclein was not a chemical unit, but rather an indefinite mixture of organic phosphorus compounds with proteid matter; but we now know, thanks to the painstaking work of Kossel and others, that there are a group of closely related bodies, *nucleins*, widely distributed in nature, wherever cell structure is to be found, as the main constituent of the cell nucleus, and likewise present in certain substances such as milk and egg-yolk which serve as food for developing animals. The latter class are better known as nucleo-albumins, from which a typical nuclein can be separated or rather prepared by the proteolytic action of the gastric juice,[6] which dissolves away the excess of proteid matter leaving a non-digestible nuclein. The essential points of difference between the typical nucleins are made clear by a study of their cleavage products. Thus, the nuclein found in the karyoplasm of most cell nuclei on being boiled with dilute sulphuric acid, yields as cleavage products, phosphoric acid, xanthin bodies and acid-albumin. The nuclein, on the other hand, present in the sperm of the salmon fails to yield any albuminous matter, its cleavage products being only phosphoric acid and hypoxanthin. The third group of nucleins, better known as nucleo-albumins, yield only phosphoric acid and albuminous bodies by cleavage, the xanthin bases, if formed, being in too small quantity to admit of certain detection. From the nuclein of yeast cells, Liebermann obtained by cleavage metaphosphoric acid, and both he[7] and Pohl were able to prepare a combination of metaphosphoric acid with egg-albumin, also with serum-albumin and with albumose, resembling nuclein in properties. Furthermore, by varying the proportions of acid and albumin it is possible to prepare different forms of nuclein, varying in their content of phosphorus, and in their solubility in alkalies, like the natural nucleins obtainable from cell nuclei. It is questionable, however, whether these synthetical products are in every way akin to the natural nucleins, for it seems probable that the nuclein molecule formed through the activity of the living cells is constructed on a somewhat different plan, so far as the arrangement of the atoms is concerned. Thus, Altman[8] has shown that when a nuclein is subjected to a mild process of decomposition, as on exposure to the action of an alkali at ordinary temperature, it is broken apart into albumin and a peculiar acid rich in phosphorus, to which the name of nucleic acid has been given. Moreover, it is possible to regenerate the nuclein out of these two components, the body so reconstructed having all the properties of the original substance. Nucleins, therefore, to quote Halliburton, may be considered as compounds of proteid substances with nucleic acid, the various members of the group differing in the proportion of proteid matter to this phosphorus-rich acid. Thus, we may have a chain of nucleins, one end of the series being represented by nucleic acid itself with its 9 to 11 per cent. of phosphorus and without any admixed proteid, such for example as is found in the heads of the spermotozoa, which are doubtless derived from the nuclei of the spermatogenic cells; while in the middle of the series are the nucleins proper consisting of proteid with varying amounts of nucleic acid, and at the other extreme nucleins composed almost entirely of proteid, containing at the most only 0.5 to 1.0 per cent. of phosphorus and represented by the substances generally known as nucleo-albumins.

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[6] Compare Lilienfeld Du Bois Reymond's Archiv f. Physiol. 1892, p. 129.

[7] Liebermann. Pflüger's Archiv für physiologie Bd. 43 p. 99.

[8] Ueber Nucleinsäuren. Du Bois Reymond's Archiv für Physiol, 1889, p. 524.

Nucleins are not digestible in artificial gastric juice, while a nucleo-albumin, as already stated, undergoes a partial digestion, the excess of combined proteid matter being converted into soluble products, while a typical nuclein remains as an insoluble residue, which however may be dissolved by weak alkalies. With this understanding of the general character of of the nucleins, many of the micro-chemical observations recorded by different workers in cytology become intelligible. Take as an illustration the work of Zacharias[9] on vegetable cells. This observer, as you remember, made a large number of digestive experiments with artificial gastric juice, and noted the occurrence in the nucleus of two distinct substances indigestible in pepsin-acid solution, which differed from each other in their solubility in acids and alkalies. As a result, Zacharias states that the resting cell nucleus consists of a ground mass composed in great part of nuclein, while the nucleoli consist of albumin and plastin. Remove the albumin from the nucleus by digestion, and the nuclein will dissolve in dilute alkali, leaving a network of plastin. Further, Zacharias states that plastin is an essential constituent of the total protoplasmic content of the cell, including the nucleus and the chromatophore. Now, note the differences between the nuclein and the plastin as defined by Zacharias. Plastin,

[9] Botanische Zeitung. 45th Jahrgang, pp. 281 and 329.

for example, does not dissolve or even swell up in 10 per cent. salt solution, hence it is not a globulin or simple proteid; further, it does not disappear on treatment with hydrochloric acid of moderate strength, as nuclein does. Again, plastin is much more difficultly soluble in alkalies than nuclein. Now as a matter of fact these two bodies have an extremely close relationship; they are both nucleins, having the same general type of structure; they differ merely in the proportion of nucleic acid and proteid. The plastin of the histologist, therefore, is simply a form of nuclein, less acid in character because it contains less nucleic acid and a larger proportion of proteid; hence, it likewise contains less phosphorus and for the same reason is more insoluble in alkalies.

In a general way we may say that the so-called nuclear sap or nuclear matrix is composed practically of a globulin-like body, just such as is found in the cytoplasm and which by digestion with artificial gastric juice is converted into soluble products, as proteose and peptone. The bulk of the nucleus, however, is composed of material insoluble in gastric juice. The bodies composing this indigestible matter are all phosphorized; in fact, they are nucleins of various kinds. Thus, the so-called chromatin network which is distinguishable from all other constituents of the cell by its strong affinity for various dyes is composed of a nuclein rich in phosphorus, viz.: a nuclein with a large content of nucleic acid and a corresponding smaller content of proteid. The nucleoli, on the other hand, which have a less pronounced affinity for dyes than the chromatin, are composed mainly of the so-called plastin, *i. e.* a nuclein comparatively poor in phosphorus and not readily soluble in alkalies. In other words, and this I think is the point deserving of special emphasis, the cell nucleus in all cells is composed mainly of nucleins, compound bodies made up of proteid matter and nucleic acid, the latter rich in phosphorus, the individual parts of the nucleus varying somewhat in accord with the varying character of the nucleins as determined by the proportions of proteid to nucleic acid. That is to say, "in the processes of vital activtiy there are changing relations between the phosphorized constituents of the nucleus, just as in all metabolic processes there is continual interchange, some constituents being elaborated, others breaking down into simpler products."[10] We are not to forget, however, that these bodies may possibly be fragments of still more complex molecules resident in the living karyoplasm of cell nuclei. In any event, the character of these fragments, if such they are, must tell us something as to the nature of the original molecules, and consequently on the basis of the above statements we may reasonably argue the probable existence of different, though closely related, chemical varieties of karyoplasm as peculiar to the cell nuclei of individual organs and tissues.

Lilienfeld,[11] however, while accepting in a general way the views already expressed emphasizes the probability that as a rule there is a constant difference between the nucleus and the body of the cell, in that the former in every phase of life consists mainly of nuclein substances, *i. e.*, nucleo-proteids, nuclein and in extreme cases nucleic acid, while the body of the cell is composed mainly of pure proteids and nucleo-albumins with a low content of phosphorus. But as there are changing relations between these individual bodies, the tone of color obtainable by different dyes is obviously more or less variable; but as a rule, we may say that the nuclein-containing bodies of the nucleus have the strongest affinity for basic dyes, while the proteids of the cell body naturally seize hold of the acid dyes.

Further, Lilienfeld, who has recently made a thorough study of the inner structure of leucocytes and has named the characteristic constituent of the nucleus, *nucleo-histon*, describes this body as a nucleo-proteid, a body comparable to a chemical salt composed of a proteid base, histon, and a complex acid, leukonuclein, which in turn is made up of nucleic acid and proteid. So that in this the latest work in this direction that I am familiar with, we find results all bearing out the general statements just submitted.[12] Again, Lilienfeld has shown that it is the nucleic acid of the nucleus which is the primary cause of the pronounced color shown by this portion of the cell on treatment with aniline dyes.

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[10] Halliburton

[11] Verhandlungen der Berliner physiologischen Gesellschaft. Du Bois Reymond's Archiv für Physiologie. Jahrgang, 1893, p. 391.

[12] Compare Lilienfeld "Zur Chemie de Leucocyten." Zeitschr. Phyiol. Chem. Band. 18, p. 473.

With this understanding of the wide-spread distribution of nucleins throughout all animal and vegetable cells, let us consider somewhat more in detail the character of their decomposition or cleavage products, for this may give us a clearer insight into their general nature. As already stated, the nucleins thus far studied yield on treatment with dilute mineral acids a row of peculiar crystalline nitrogenous products, the xanthin bases so-called, the true antecedent of which Kossel has shown to be nucleic acid. Hence, the yield of these bodies, which, by the way, belong to the uric acid group, must depend upon the amount of nucleic acid contained in the given nuclein. The wide-spread distribution of these bodies, throughout the animal organism especially, wherever cell activity is pronounced, their close connection with uric acid and their evident origin in the nucleic acid of cell nuclei are facts of great physiological importance, since they throw possible light upon the physiological function of the cell nucleus and at the same time point to a genetic connection between the nuclein bases and uric acid. This phase of the matter, however, we cannot now consider, but there are one or two points connected with these nuclein bases that we cannot afford to pass by. First, the bases themselves are four in number, viz.: adenin, guanin, xanthin and hypoxanthin, all well defined bodies of known chemical constitution. Among these, adenin stands foremost. It is, to be sure, the one most recently discovered, but its characteristic chemical nature and constitution give it a peculiar prominence the others do not possess. It is not only a product of the chemical decomposition of pure nuclein by dilute acids, but it is widely distributed in nature, and its distribution in the organs and tissues of animals and plants corresponds to its genetic relationship to the characteristic constituent of the cell nucleus. Thus Kossel[13] has obtained it from the pancreatic gland and from the spleen, also from yeast cells and from tea leaves, but found it

[13] Zeitschrift für physiologische Chemie. Band 12, p. 241.

wanting in muscle tissue, poor in nuclei. F. Kronecker[14] found it in the spleen, lymph glands and kidneys of oxen, while Stadthagen[15] found it present in the liver and urine of a patient suffering from leukæmia, a disease in which the white blood cells are enormously increased in number. It is not to be understood, however, that the adenin exists wholly free in these cases. On the contrary, it exists in plant and animal tissues in loose combination, in part at least, with albumin and phosphoric acid. This combination is easily broken by the action of dilute acids, especially at 100° C., and also by spontaneous decomposition after death, *i. e.*, the adenin is an integral part of the nucleic acid which is present in all cell nuclei, and under certain conditions can be split off from the complex molecule of which it is an integral part.

In composition, adenin is peculiar in that it contains no oxygen. It is composed solely of carbon, hydrogen and nitrogen in such proportion as to warrant the conclusion that it is a polymer of prussic acid, HCN. It has in fact the same percentage composition as prussic acid, and its ready convertibility into potassium cyanide by fusion with caustic potash at 200° C., testifies to the close relationship between these two bodies. The existence of cyanogen compounds in the animal body has long been suggested as theoretically probable, and the finding of adenin gives to this hypothesis a substantial basis and points to the cell nucleus as the seat of these cyanogen compounds. Further, adenin is closely related to hypoxanthin, a body with which we are more familiar and whose origin we shall need to consider. Moreover, we find when we come to study relationships that all the so-called nuclein bases are closely related to adenin, as is seen from the following formulæ, which bring out the analogies quite clearly:

| | | | |
|---|---|---|---|
| Adenin | $C_5H_4N_4\ NH$ | Guanin | $C_5H_4N_4O\ NH$ |
| Hypoxanthin | $C_5H_4N_4\ O$ | Xanthin | $C_5H_4N_4O\ O$ |

Both adenin and hypoxanthin contain a peculiar chemical group $C_5H_4N_4$, called by Kossel and Thoiss[16] adenyl, and we may consequently consider adenin as adenylimid, while hypoxanthin may be appropriately termed adenyloxide. As might be expected from the close relationship between these two bodies, adenin can be readily converted into hypoxanthin; and in a similar manner the allied base guanin can be transformed into xanthin. Thus, Schindler[17] finds by experiment that adenin dissolved in water and exposed to putrefaction at about 20° C. with exclusion of air, in time entirely disappears, a large amount of hypoxanthin appearing in its place and likewise a trace of xanthin. In other words, oxygen-free adenin is made by this process to combine with oxygen, being converted into the related oxygen-containing body hypoxanthin, with a giving up of ammonia. Guanin by a like method of treatment is changed into xanthin. The reactions involved are very simple as the following equations show :

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[14] Virchow's Archiv. Band 107, p. 207.

[15] Ibid. Band 109, p. 390.

[16] Zeitschrift für physiologische Chemie. Band 13, p. 396.

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_5H_5N_5$ | $+$ | $H_2O$ | $=$ | $C_5H_4N_4O$ | $+$ | $NH_3$ |
| Adenin | | | | Hypoxanthin | | Ammonia |
| $C_5H_5N_5O$ | $+$ | $H_2O$ | $=$ | $C_5H_4N_4O_2$ | $+$ | $NH_3$ |
| Guanin | | | | Xanthin | | Ammonia |

We thus have every reason for believing that when hypoxanthin results from the breaking down of nuclein it passes through the intermediate stage of adenin. In other words, adenin is a primary cleavage product of nuclein, or rather of nucleic acid, while hypoxanthin is a secondary product coming directly from the adenin. In a similar manner, guanin is a primary decomposition product of nucleic acid, xanthin being in the same sense a secondary product. These four bases are plainly closely related and intimately associated in many ways, and all are alike cleavage products of the nuclein obtainable from cell nuclei. But the primary bodies adenin and guanin are evidently far more susceptible to the changes going on in living cells than their neighbors hypoxanthin and xanthin. All four, however, are capable of complete decomposition with formation of a variety of decomposition products. In this connection, one of the most instructive series of changes adenin undergoes outside the body is that induced by long-continued warming with dilute hydrochloric acid, in which it is completely broken down into ammonia, carbonic acid, formic acid and glycocoll or amido-acetic acid. Xanthin and hypoxanthin furnish the same products by like treatment:

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[17] Zeitschrift für Physiologische Chemie. Band 13, p. 432.

$$C_5H_5N_5 + 8H_2O = 4NH_3 + CO_2 + 2H\text{–}COOH + CH_2\text{–}NH_2\text{–}COOH$$

Adenin. Formic Acid. Glycocoll.

$$C_5H_4N_4O + 7H_2O = 4NH_3 + CO_2 + 2H\text{–}COOH + CH_2\text{–}NH_2\text{–}COOH$$

Hypoxanthin.

$$C_5H_4N_4O_2 + 6H_2O = 3NH_3 + 2CO_2 + H\text{–}COOH + CH_2NH_2\text{–}COOH$$

Xanthin.

Again, adenin can be easily decomposed completely into carbonic acid and ammonia, but the most striking fact in connection with this body, as already stated, is its easy convertibility into cyanide of potash, indicating as it does the close relationship existing between this substance and the cyanogen group.

In attempting to ascribe a function to adenin that shall correspond to the accepted function of the cell nucleus, we must have proof that this substance, under conditions which obtain in the body can readily pass into new forms easily capable of undergoing reactions. As has been shown by experiment, the conditions for vigorous reduction processes are present in every cell. Reduction gives a blow by which the oxygen-free adenin may be transformed into a new body having a strong avidity for oxygen, and which may in turn be transformed through the laying on of more molecules into a body resembling, if not identical with, azulminic acid. Adenin, for example, dissolved in dilute hydrochloric acid and treated with zinc is quickly decomposed by the reducing action of the nascent hydrogen evolved into what is evidently azulminic acid $C_4H_5N_5O$, a derivative of dicyan. If dicyan $\begin{array}{c}CN\\ |\\ CN\end{array}$

is simply dissolved in water and allowed to stand exposed to the air for a long time, the solution gradually becomes dark in color, accompanied by a dissociation in which formic acid, prussic acid, oxalate of ammonia and urea result, together with a certain amount of azulminic acid; reactions which again emphasize the cyanogen-like character of the adenin molecule.

Such being the nature of adenin, it is not to be doubted that bodies emanating from this substance with strong affinities must be important actors in the physiological and chemical processes, especially those of a synthetical order,.going on in all cellular tissues. In this connection it is to be remembered that Pflüger on purely theoretical grounds ascribed great importance to the physological rôle played by the cyanogen group with polymerization, etc., in the living albumin molecule. Dead albumin, such as we see in the white of egg, blood-fibrin, etc., is a comparatively stable substance, indifferent to neutral oxygen, not readily prone to change, and yielding decomposition products by no means identical with the cyanogen-like bodies resulting from normal proteid metabolism.[18] Evidently then the dead food-albumin in being assimilated is reconstructed on a different plan, the atoms are rearranged and in the living albumin molecule, as in the protoplasm of the cell, we are lad to infer a close union of the carbon and nitrogen with formation of the comparatively unstable cyanogen group. In the dead protoplasm, on the other hand, the nitrogen of the proteid is joined directly with hydrogen to form amidogen ($NH_2$), but in the processes of anabolism going on in all living cells, the nitrogen is detached from the hydrogen and made to combine more directly with carbon to form the more unstable group CN. As a result, the katabolic products of proteid metabolism known to us are the cyanogen-containing bodies, guanin, uric acid, creatin and the related body urea. These are products of the katabolism of living protoplasm, and in the discovery of adenin and its close relationship to the typical xanthin bases we have added proof of the existence of cyanogen-containing radicals in the protoplasm of the cell, especially in the karyoplasm of the nucleus. In all of these xanthin bodies there is to be seen a peculiar combination of carbon, nitrogen and hydrogen such as is not found in dead proteid matter. The structure of the molecule is different and is emblematical of a still more complex molecule in which the atoms are similarly arranged.

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[18] See Drechsel, however, Der Abban der Eiweissstoffe. Du Bois Reymond's Archiv, 1891, p. 248.

Thus, it is to be remembered that whenever an organ rich in cells is decomposed by dilute acid, adenin, guanin, xanthin and hypoxanthin are never obtained alone. They are not found as individuals, but in every tissue which has retained its original condition, the two special xanthin bases, for example, are found in combination with other groups of atoms, especially with phosphoric acid and albumin, as parts of a higher compound, the nuclein. From this higher compound, the individual components cannot be extracted by simple solvents or other like methods of isolation; a blow must be struck by which the complex molecule shall be shattered and the individual parts liberated, as by the action of a dilute mineral acid. In tissues very poor in nuclear elements, on the other hand, as in muscle tissue, we find only the decomposition products of nuclein; the chemical union between the individual fragments is broken, and the phosphoric acid, for example, no longer exists in organic combination, but as soluble alkali phosphates. In a similar manner, the xanthin and hypoxanthin exist in a free condition capable of extraction by water alone.

Further, in the transformation of adenin and guanin into hypoxanthin and xanthin respectively, with a splitting off of the NH group and the acquisition of oxygen we have a possible illustration of the manner in which the migration of the amidogen group of albumin to urea takes place; a transformation which no doubt goes on in the tissues and perhaps in every cell nucleus.

Certainly then in the light of what has been said, the cell nucleus may be looked upon as in some manner standing in close relation to those processes which have to do with the formation of organic substances. Whatever other functions it may possess, it evidently, through the inherent qualities of the bodies entering into its composition, has a controlling power over the metabolic processes going on in the cell, modifying and regulating the nutritional changes.[19] And you will notice that I lay great stress upon the chemical nature of the karyoplasm, the inherent qualities of the plasm as indicated by its molecular condition. It is not the mere fact that the karyoplasm is housed, so to speak, in a certain definite structure that it is possessed of its characteristic qualities, but the qualities are peculiar to the living molecules themselves. The living molecules are different from the dead molecules because they have a different chemical constitution, the atoms are arranged in a different manner. All this being true we can easily see how cells devoid of specific nuclei may perhaps be functionally active, to a slight extent, provided they contain the same chemical groups in the cytoplasm.

But I have already exceeded the alloted time, while there is much that might be said. Still, the foregoing will indicate in a limited way that there is a field of work in connection with the chemistry of the cell that cannot consistently be ignored in biological inquiries.

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[19] Compare M. Verworn, "Die physiologische Bedeutung des Zellkerns." Pflüger's Archiv f. Physiol. Band 51, p. 1.